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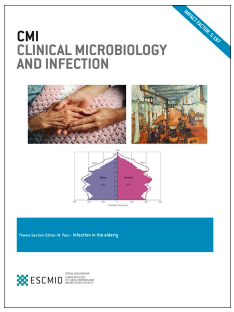

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Predictors for treatment outcomes among patients with drug-susceptible tuberculosis in the Netherlands: a retrospective cohort study

Ivan S. Pradipta[1,2,3], Natasha van't Boveneind-Vrubleuskaya[3,4], Onno W. Akkerman[5,6], Jan-Willem C. Alffenaar[3], Eelko Hak[1]

[1] University of Groningen, Groningen Research Institute of Pharmacy, Unit of Pharmaco-Therapy, -Epidemiology and -Economics (PTE2), The Netherlands
[2] Department Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Indonesia
[3]University of Groningen, University Medical Centre Groningen, Department of Clinical Pharmacy and Pharmacology, The Netherlands
[4] Department Public Health TB Control, Metropolitan Public Health Services, The Hague, The Netherlands
[5]University of Groningen, University Medical Centre Groningen, Department of Pulmonary Diseases and Tuberculosis, Groningen, The Netherlands
[6]University of Groningen, University Medical Centre Groningen, Tuberculosis Centre Beatrixoord, Haren, The Netherlands

*Corresponding author:
Ivan S. Pradipta, M.Sc., PharmD.
University of Groningen, Groningen Research Institute of Pharmacy,
PharmacoTherapy, - Epidemiology & -Economics,
P.O. BOX. 196, 9700 AD Groningen, The Netherlands
Ph. +31 50 361 7870
Email : ivanpradipta@unpad.ac.id / i.s.pradipta@rug.nl.

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ABSTRACT

Objectives: We evaluated treatment outcomes and predictors for poor treatment outcomes for tuberculosis (TB) among native- and foreign-born patients with drug-susceptible TB (DSTB) in the Netherlands.

Methods: This retrospective cohort study included adult patients with DSTB treated from 2005 to 2015 from a nationwide exhaustive registry. Predictors for unsuccessful treatment outcomes (default and failure) and TB-associated mortality were analysed using multivariate logistic regression.

Results: Among 5,674 identified cases, the cumulative incidence of unsuccessful treatment and mortality were 2.6% (n/N = 146/5,674) and 2.0% (112/5,674), respectively. Although most patients were foreign-born (71%; 4,042/5,674), no significant differences in these outcomes were observed between native- and foreign-born patients ($p > 0.05$). Significant predictors for unsuccessful treatment were age of 18–24 years [odds ratio (OR), 2.04; 95% confidence interval (CI): 1.34–3.10], homelessness (OR, 2.56; 95% CI: 1.16–5.63), prisoner status (OR, 5.39; 95% CI: 2.90–10.05) and diabetes (OR, 2.02; 95% CI: 1.03-3.97). Furthermore, predictors for mortality were age of 74–84 (OR, 5.58; 95% CI: 3.10–10.03) or ≥85 years (OR, 9.35, 95% CI: 4.31–20.30), combined pulmonary and extra-pulmonary TB (OR, 4.97; 95% CI: 1.42–17.41), central nervous system (OR, 120, 95% CI: 34.43–418.54) or miliary TB (OR, 10.73, 95% CI: 2.50–46.02), drug addiction (OR, 3.56; 95% CI: 1.34–9.47) and renal insufficiency/dialysis (OR, 3.23; 95% CI: 1.17–8.96).

Conclusions: Native- and foreign-born patients exhibited similar TB treatment outcomes. To further reduce disease transmission and inhibit drug resistance, special attention should be given to high-risk patients.

Keywords: Risk factors, Treatment outcome, Tuberculosis, The Netherlands, Epidemiology.

Introduction

Although tuberculosis (TB) is a global health problem [1], the associated burden in Europe has been mainly attributed to the travel and migration of people from high- to low-TB burden countries [2–4]. Several groups, including immigrants, asylum seekers, prisoners and homeless individuals, have been identified as high-risk groups [4,5]. Hence, adequate treatment management is required, especially for high-risk groups.

The Netherlands has a low TB incidence, with an estimated incidence of 5.9/100,000 population in 2016 [5]. According to the Netherlands Tuberculosis Registry (NTR), drug-susceptible TB (DSTB) is the most common form of TB in the Netherlands. From 2005 to 2015, 72% of cases (n/N= 7,416/10,303) were identified as using standard treatment for DSTB. A previous study from the Netherlands (1993–1997) identified a higher probability of treatment default among asylum seekers, immigrants and illegal immigrants [6]. However, updated data are needed to determine whether being in a risk group or other factors contribute to poor outcomes of TB treatment and to evaluate the success of current treatment programmes in the Netherlands. We therefore aimed to evaluate treatment outcomes and predictors for poor treatment outcomes for tuberculosis (TB) among native- and foreign-born patients with drug-susceptible TB (DSTB) in the Netherlands.

Methods

Study design and setting

This retrospective cohort study included patients treated for DSTB between 1 January 2005 and 31 December 2015. Anonymised data were obtained from the NTR database on 23 January 2017 following approval from the NTR committee. The NTR is an exhaustive national database managed by the Dutch National Institute for Public Health and the Environment (RIVM). Real-time surveillance data are routinely collected by RIVM in close collaboration with the TB control department of the Municipal Public Health Services (MPHS) and Royal Netherlands Tuberculosis Association/ KNCV TB. MPHS are legally required to record and register all patients with TB in the Netherlands, including those treated in hospitals. NTR data collection occurs throughout the TB diagnostic and treatment period, and the information is entered by the physician or nurse into an electronic report via the Online Registration System for Infectious Diseases in Infectious Diseases Surveillance Information System (OSIRIS) after the diagnosis is made. KNCV TB and MPHS check the registrations for completeness and consistency through an interactive process. MPHS receives reminders when records remain incomplete. The online system enables MPHS to correct and add information to patient records.

Study subjects

We included patients with TB aged ≥18 years who were registered in the NTR database and classified as being infected with *Mycobacterium tuberculosis* strain that was considered fully sensitive to first-line anti-TB drugs and treated during the study period. From this cohort of eligible patients, those with an unknown treatment outcome, i.e. no treatment initiated, treatment ongoing and treatment continued elsewhere with unknown results during a 1-year period, were excluded.

Potential predictors and definitions

Potential predictors for a poor outcome of TB treatment were identified at baseline (before or during diagnosis) to predict the incidence of the study outcome. We selected a set of potential predictors based on previously published articles (see **Supplementary 1**), input from TB practitioners and information from the NTR database. These potential predictors were classified into five categories: (1) socio-demographic characteristics (age, sex, birth country, domicile area, insurance coverage for TB), (2) current TB diagnosis (pulmonary TB type, TB location, place of diagnosis, treatment delay), (3) history of TB disease and treatment [previously diagnosed TB, treated latent TB infection (LTBI), Bacillus Calmette–Guérin (BCG) vaccination status] (4) risk groups (those in contact with patients with TB, immigrants, asylum seekers, illegal immigrants, homeless individuals, healthcare workers, travellers from/in endemic area, prisoners, alcohol and drug addicts) and (5) high-risk comorbidities [diabetes, human immunodeficiency virus (HIV), malignancy, renal insufficiency/dialysis, organ transplantation].

Primary outcomes

We retrospectively followed patients from the beginning to the end of DSTB treatment for one episode of TB during a 1-year period. According to the WHO criteria [7], we categorised the study outcomes into unsuccessful treatment and TB-associated mortality. Unsuccessful treatment was defined as a combination of defaulted and failed treatment. Treatment default cases met one of the following four conditions: interruption of TB treatment for ≥2 consecutive months, incomplete treatment for 6 months within a 9-month treatment period, incomplete treatment for 9 months within a 12-month treatment period and completion of <80% of the treatment. Failed treatment was defined as a positive sputum smear or culture at 5 months or more after treatment initiation. For extra-pulmonary TB, treatment failure was defined by a physician according to a national guideline [8]. All treatment outcomes were determined by a physician in daily clinical practice. The operational definitions of these

variables followed those in the manual OSIRIS guideline published by RIVM [9] (**Supplementary Table S1**).

Statistical analysis

Distributions of subjects' characteristics and the cumulative incidences were examined using descriptive statistics. The cumulative incidence of the study outcomes were calculated by dividing incidence of the outcome with the number of DSTB cases during the observation period. We eliminated potential predictors if >10% of the data were missing. We used the chi-square test or Fisher's exact test (when expected cell size was <5) for univariate analyses of categorical covariates. Variables with a p-value of <0.25 in the univariate analysis were considered for inclusion in the multivariate analysis. If the number of variables exceeded the assumption of 10 events per variable examined, we considered a stricter univariate p-value (<0.15) for inclusion in the multivariate analysis [10]. To increase the statistical power and validity, we minimised the degree of freedom in the predictor model by combining predictors that measured a similar concept and had similar estimated risks in the univariate analysis [10]. Variables for which there were no incidences of the study outcome in the indicator group were not included in the multivariate analysis. A backward step elimination based on a p-value of >0.05 was used for the multivariate analysis. We used complete case analysis that excluded patients with missing values [10]. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to quantify the level of association between variables and outcomes. The calibration of the multivariate analysis model was assessed using the Hosmer–Lemeshow test, while discrimination was estimated using a receiver operating characteristic curve with a 95% CI. We used Statistical Package for the Social Science, version 23 (SPSS; IBM Corp., NY, USA) for Windows™ in all statistical analyses; a final p-value of <0.05 was considered significant in the multivariate analysis. We followed the STROBE guidelines for reporting this study [11].

Result

Baseline characteristics of study subjects

Of the 10,303 adult cases with TB registered during the study period, we identified 5,674 cases with DSTB who fulfilled the study criteria (**Figure 1**). Most patients with DSTB were foreign-born (71%, n/N = 4,042/5,674; **Table 1**). As described in **Figure 1**, 192 patients with DSTB were lost to observation and had missing information about treatment outcomes. Missing information about TB treatment outcomes was significantly more frequent ($p < 0.05$) among males, foreign-born patients, prisoners, those with pulmonary TB, those with TB diagnosis from outside the Netherlands, immigrants, illegal immigrants and those with a history of travel from/to an endemic area >3 months earlier (**Supplementary Table S2**).

Incidence of DSTB

We observed a significant declining trend in the number of DSTB cases within the study period ($p <0.05$), with cumulative incidences of unsuccessful TB treatment and TB-associated mortality as 2.6% (146/5,674) and 2.0% (112/5,674), respectively. The highest annual cumulative incidence for both these outcomes was identified in 2011 (**Fig. 2**).

Predictors for outcomes

We combined asylum seekers and immigrants as one covariate in the analysis because similar residential status outside the Netherlands was thought to yield relatively similar statistical associations in the univariate analysis. In the univariate analysis, immigrants and asylum seekers had ORs (95% CI) of 0.90 (0.48–1.67) and 1.57 (0.97–2.54) for unsuccessful treatment outcome, while for mortality outcome had ORs (95% CI) of 0.19 (0.05–0.80) and 0.09 (0.12–0.62), respectively.

In the univariate analysis, sex, age, homelessness and prisoner status were significantly associated ($p < 0.05$) with unsuccessful treatment. Furthermore, multivariate analyses revealed a final prediction model comprising age of 18–24 years (OR, 2.04; 95% CI: 1.34–3.10), homelessness (OR, 2.56; 95% CI: 1.16–5.63), prisoner status (OR, 5.39;

95% CI: 2.90–10.05) and diabetes (OR, 2.02; 95% CI: 1.03–3.97) as significant predictors for unsuccessful treatment (**Table 2**).

Regarding mortality, age; pulmonary diagnostic type; initial TB location, such as lung, CNS and miliary TB; previous TB diagnosis; non-immigrant status; non-asylum seeker; native-born status and comorbidities, such as diabetes, malignancy, renal insufficiency/dialysis and organ transplantation, were significantly associated with death in the univariate analysis ($p < 0.05$). Finally, we identified age of 75–84 (OR, 5.58; 95% CI: 3.10–10.03) or ≥85 years (OR, 9.35; 95% CI: 4.31–20.30), combined pulmonary and extra-pulmonary TB (OR, 4.97; 95% CI: 1.42–17.41), central nervous system (OR, 120; 95% CI: 34.43–418.54) or miliary TB (OR, 10.73; 95% CI: 2.50–46.02), drug addiction (OR, 3.56; 95% CI: 1.34–9.47), renal insufficiency/dialysis (OR, 3.23; 95% CI: 1.17–8.96) and immigrant or asylum seeker status (OR, 0.11; 95% CI :0.01–0.84) as significant predictors for mortality (**Table 3**).

Discussion

Although most cases in our study involved foreign-born patients, no significant differences in treatment outcomes were observed between native- and foreign-born patients. Immigrants and asylum seekers had a lower risk of death than other patients and no significant difference in the risk for unsuccessful TB treatment. Overall, approximately 5 in 100 treated DSTB cases had a poor TB treatment outcome, of which 2.6% (146/5,674) were attributed to unsuccessful treatment and 2.0% (112/5,674) to TB-associated mortality. Predictors for unsuccessful treatment included age of 18–24 years, homelessness, prisoner status and diabetes. Furthermore, age of ≥75 years, drug addiction, combined pulmonary and extra-pulmonary TB and several comorbidities [renal insufficiency, central nervous system (CNS) and miliary TB] were predictors for TB-associated mortality. Moreover, male sex, foreign-born patients, immigrants, illegal immigrants, travellers from/in endemic areas for >3 months, those diagnosed with TB from outside of the Netherlands, those with pulmonary TB and prisoners were more likely to be lost to treatment follow-up which indicates potential high risk of poor outcomes.

Diabetes was identified as a risk factor for unsuccessful TB treatment in this study. Previous studies have demonstrated that the correlation of diabetes with TB treatment failure [12] could be attributed to altered drug absorption [13] and immune system as well as drug interaction [14]. We further identified renal insufficiency/dialysis as a risk factor for TB-associated mortality. In patients undergoing dialysis, altered immune response associated with uraemia and dialysis exacerbation have been identified as predisposing factors for active TB development [15]. Patients with end-stage renal disease are more susceptible to TB [16]. Furthermore, drug-induced hepatitis has been identified more frequently in patients with TB and chronic renal failure than in those with TB but without chronic renal failure that increase the risk of TB-associated mortality [17].

Our finding of age being a relevant predictor was supported by a retrospective population-based pulmonary TB study in a South African province, in which younger patients

(age <25 years) more likely defaulted treatment [18]. Moreover, a multi-centre prospective cohort study in Spain reported that elderly people were more likely to die from TB [19].

A previous Dutch study (1993–1997) showed an association between the risk of treatment default and being in the high-risk group (asylum seekers, immigrants, illegal immigrants, homeless individuals, prisoners and eastern European nationals) [6]. However, the present study did not show that immigrants and asylum seekers as a high-risk group in terms of outcomes (unsuccessful treatment and TB-associated mortality). It seems that asylum seekers and immigrants received a successful treatment during the study period.

According to the national guideline, immigrants and asylum seekers comprise a high-risk priority group for TB screening and monitoring [20]. People from TB-endemic countries who plan to reside in the Netherlands for >3 months are required to undergo regular chest X-ray for 2 years. TB diagnosis leads to the administration of regular treatment and monitoring, together with treatment support from a nurse at Municipal Public Health Services. To ensure TB treatment compliance, municipal health centres work closely with medical service providers to asylum seekers and prisoners as well as with social workers from institutions for homeless care. Total TB control expenditures are covered by health insurance and funding from municipal authorities and the government [21]. For uninsured patients, the treatment cost is covered by municipalities via the public health act or budgeted financial support for illegal immigrants [22]. Two modern TB hospitals have been established for the long-term admission and specialised treatment of clinically complex or socially problematic TB cases to support successful treatment [23]. TB management is standardised according to a national TB guideline [8] and framework of the National Tuberculosis Control and Plan [21].

We identified homeless individuals and prisoners as being at a risk of unsuccessful TB treatment and drug addicts as a dominant risk group for TB-associated mortality. These vulnerable and hard-to-reach patients have both individual problems and challenges related to healthcare facility access. Specifically, individuals in these groups lack awareness and knowledge of TB and experience stigma, unstable accommodation and challenges in terms of transportation, costs and treatment duration [24]. Furthermore, drug users are frequently

297 homeless individuals, prisoners or HIV-positive [25], all of which further increase the risk of
298 poor TB treatment outcome. Therefore, hard-to-reach patients should be admitted into a
299 modern TB hospital to intensify treatment and monitoring and enable successful outcomes.

300 Our results were inconsistent with those of several other local studies regarding the
301 determinants for poor TB treatment outcomes in Pakistan [26], China [27], South Korea [28],
302 and Germany [29]. For instance, a study in Hamburg identified alcohol dependence as a
303 determinant for disease persistence and treatment interruption. These inter-study differences
304 can be explained by differences in risk factors across settings due to differences in
305 healthcare systems, government support and patients' social, clinical and behavioural
306 characteristics. Previous analyses also included subjects with drug-resistant TB, a specific
307 high-risk group that requires longer and other treatment, and more study on their prognosis is
308 needed.

309 Several potential limitations need to be acknowledged. First, because we used data
310 from an administrative database, our dataset relied on reports from clinicians without any
311 direct observations by current investigators, which may have led to inaccuracies. Second,
312 several prominent predictors which may have further increased the discriminative value of
313 multivariate models, such as HIV, treatment delay duration, BCG vaccination history,
314 insurance coverage, education level, income and patient beliefs, could not be analysed due
315 to unavailability of data for a large number of patients. Third, a low mortality rate in this study
316 led to low precision of the associations between mortality outcome and some predictors,
317 such as age and initial TB location (CNS and miliary TB). However, we believe that the
318 systematic approach for data collection supported by information technology, national
319 guideline, control system for data collection and an integrated referral system for patients
320 with TB in the Netherlands led to a minimal bias in this study. Importantly, expanding the
321 national database coverage to include patients throughout the Netherlands will improve the
322 applicability of our results to the Dutch DSTB population.

323 In conclusion, although most DSTB cases included foreign-born patients, these
324 patients achieved similar TB treatment success compared with native-born patients. We

observed a relatively low incidence of unsuccessful TB treatment and TB-associated mortality among DSTB cases in the Netherlands. However, to reduce further disease transmission and inhibit drug resistance, the potential for unsuccessful treatment should be considered among patients with DSTB aged 18–24 years and those who are homeless, prisoners or diabetic. Furthermore, patients aged ≥75 years, drug addicts, those diagnosed with CNS TB, miliary TB, renal insufficiency comorbidity, combined pulmonary and extra-pulmonary TB should be carefully monitored to prevent premature mortality. Further study is needed to investigate the quality of TB management, barriers and effective interventions for improved treatment in high-risk groups.

Transparency declaration

Conflict of Interest

All authors report no conflicts of interest relevant to this article.

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Contributions

All the authors designed the study. ISP, EH and JWA analysed the data. ISP wrote the first draft of the article. All the authors revised the article and approved the final version.

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FIGURES AND TABLES

Figure 1. Flow diagram of the included subjects. *M. tb, Mycobacterium tuberculosis*; H, isoniazid; R, rifampicin; E, ethambutol; Z, pyrazinamide; MDR, multi-drug-resistant; XDR, extensively drug-resistant; DSTB, drug-susceptible tuberculosis; DRTB, drug-resistant tuberculosis.

Figure 2. Annual cumulative incidence for TB treatment outcomes during 2005–2015. DSTB, drug-susceptible tuberculosis; TB, tuberculosis

489 **Table 1**. Characteristics of subjects (N = 5,674)

No	Characteristics	Frequency (%)
1	**Socio-demographic**	
	Male	3,426 (60.4)
	Age (years):	
	18–24	867 (15.3)
	25–74	4,246 (74.8)
	75–84	422 (7.2)
	≥85	139 (2.4)
	Country of birth*:	
	The Netherlands	1,617 (28.5)
	Somalia	741 (13.1)
	Maroco	539 (9.5)
	Indonesia	275 (4.8)
	Suriname	274 (4.8)
	Turkey	187 (3.3)
	Others	2,041 (36)
	Urban domicile[†]	1,997 (35.2)
	Insurance coverage for TB*[§]	57 (10.3)
2	**Current TB diagnosis**	
	Pulmonary diagnosis	
	ETB	1,890 (33.3)
	PTB	3,012 (53.1)
	ETB + PTB	772 (13.6)
	Initial TB location	
	Lungs	3,505 (61.8)
	Central nervous system	70 (1.2)
	Miliary	125 (2.2)
	Others	1,974 (34.8)
	TB diagnosis outside of the Netherlands	50 (0.9)
	Treatment delay >4 weeks*	1,053 (18.5)
3	**History of TB disease & treatment**	
	Previously diagnosed TB*	358 (6.3)
	Previously treated LTBI*	184 (3.2)
	BCG vaccination*	1,555 (27.4)
4	**TB risk group**	
	TB contact	375 (6.6)
	Immigrant	471 (8.3)
	Asylum seeker	527 (9.3)

	Illegal immigrant	201 (3.5)
	Homeless individuals	132 (2.3)
	Health care workers	46 (0.8)
	Travelers from/in endemic area >3 month	130 (2.3)
	Prisoners	143 (2.5)
	Alcohol addicts	111 (2.0)
	Drug addicts	152 (2.7)
5	**Comorbidities**	
	Diabetes	268 (4.7)
	HIV positive	229 (4.0)
	Malignancy	135 (2.4)
	Renal insufficiency/ dialysis	91 (1.6)
	Organ transplantation	22 (0.4)
6	**Outcomes**	
	Cure or completed treatment	5,190 (91.5)
	Defaulted treatment	144 (2.5)
	Failed treatment	2 (0.0)
	Death due to TB	112 (2.0)
	Death due to non-TB	226 (4.0)

Notes: *missing data : Country of birth 15 (0.3%), Previously diagnosed TB 437 (7.7%), Previously treated LTBI 466 (8.2%), BCG vaccination 2,812 (49.6%), HIV positive 3,329 (58.7%), treatment delay 4,056 (71.5), insurance coverage for TB 5,062 (89.2%); [§]the information was documented from 2014; [†]Urban domicile : Amsterdam, Rotterdam, the Hague and Utrecht; TB, tuberculosis; ETB, extra-pulmonary tuberculosis; PTB, pulmonary tuberculosis; LTBI, latent tuberculosis infection; BCG, Bacillus Calmette–Guérin; HIV, human immunodeficiency virus.

Table 2. Predictors for unsuccessful tuberculosis treatment outcome (N = 5,674)

No	Predictors	Unsuccessful treatment		Univariate analysis		Multivariate analysis*	
		No (n = 5,528; %)	Yes (n= 146; %)	OR (95%CI)	p-value	aOR (95%CI)	p-value
1	**Socio-demographic characteristics**						
	Male	3325 (60.1)	101 (69.2)	1.35 (1.04-1.76)	0.025	1.35 (0.91-2.01)	0.13
	Age (years)				0.000		0.004
	18–24	834 (15.1)	33 (22.6)	1.66 (1.11-2.48)		2.04 (1.34-3.10)	
	25–74	4147 (75)	99 (67.8)	Ref.		Ref.	
	75–84	415 (7.5)	7 (4.8)	0.71 (0.33-1.53)		0.83 (0.36-1.93)	
	≥85	132 (2.4)	7 (4.8)	2.22 (1.01-4.87)		2.24 (0.89-5.67)	
	Born in the Netherlands**	1579 (28.6)	38 (26.2)	0.89 (0.61-1.29)	0.52	Not included	-
	Urban domicile	1946 (35.2)	51 (34.9)	0.99 (0.70-1.40)	0.95	Not included	-
2	**Current TB diagnosis**						
	Pulmonary diagnosis				0.76	Not included	-
	ETB	1839 (33.3)	51 (34.9)	Ref.			
	PTB	2934 (53.1)	78 (53.4)	0.96 (0.67-1.37)			
	ETB + PTB	755 (13.7)	17 (11.6)	0.81 (0.47-1.42)			
	Initial TB location				0.11		0.52
	Lungs	3416 (61.8)	89 (61)	0.89 (0.64-1.25)		0.75 (0.52-1.10)	
	Central nervous system	70 (1.3)	0 (0)	n/a		n/a	
	Miliary	124 (2.2)	1 (0.7)	0.28 (0.04-2.01)		n/a	
	Others	1918 (34.7)	56 (38.4)	Ref.		Ref.	
	TB diagnosis outside of the Netherlands	48 (0.9)	2 (1.4)	1.59 (0.38-6.58)	0.37	Not included	-
3	**History of TB disease & treatment**						
	Previously diagnosed TB**	345 (6.8)	13 (9.8)	1.50 (0.84-2.68)	0.17	1.46 (0.75-2.81)	0.26
	Previously treated LTBI**	177 (3.5)	7 (5.3)	1.56 (0.72-3.39)	0.23	1.82 (0.83-4.00)	0.14
4	**TB risk group**						
	TB contacts	366 (6.6)	9 (6.2)	0.93 (0.47-1.83)	0.83	Not included	-
	Immigrants & asylum seekers	966 (17.5)	31 (21.2)	1.27 (0.85-1.90)	0.24	1.34 (0.84-2.14)	0.22
	Illegal immigrants	198 (3.6)	3 (2.1)	0.57 (0.18-1.79)	0.32	Not included	-
	Homeless individuals	123 (2.2)	9 (6.2)	2.89 (1.44-5.80)	0.007	2.56 (1.16-5.63)	0.02
	Health care workers	46 (0.8)	0 (0)	0.40 (0.02-6.56)	0.52	Not included	
	Travelers from/in endemic area >3 month	128 (2.3)	2 (1.4)	0.59 (0.14-2.39)	0.78	Not included	

	Prisoners	127 (2.3)	16 (11)	5.23 (3.03-9.06)	0.000	5.39 (2.90-10.05)	0.000
	Alcohol addicts	107 (1.9)	4 (2.7)	1.43 (0.52-3.93)	0.54	Not included	-
	Drug addicts	146 (2.6)	6 (4.1)	1.58 (0.69-3.64)	0.28	Not included	-
5	**Comorbidities**						
	Diabetes	257 (4.6)	11 (7.5)	1.67 (0.89-3.13)	0.11	2.02 (1.03-3.97)	0.04
	Malignancy	129 (2.3)	6 (4.1)	1.79 (0.78-4.14)	0.16	2.09 (0.81-5.35)	0.13
	Renal insufficiency/dialysis	91 (1.6)	0(0)	0.20 (0.01-3.28)	0.26	Not included	-
	Organ transplantation	21 (0.4)	1 (0.7)	1.81 (0.24-13.54)	0.44	Not included	-

Notes: *Number of analysed cases, 5,674; Hosmer & Lemeshow test, 0.99; area under the curve, 0.64 (0.59–0.69); n/a, not applicable due to a small number of events; Ref., reference; OR, odds ratio; aOR, adjusted odds ratio; **missing values: country of birth, 15 (0.3%); previous TB diagnosis, 437 (7.7%); previous LTBI treatment, 466 (8.21%); ETB, extra-pulmonary tuberculosis; PTB, pulmonary tuberculosis; TB, tuberculosis; LTBI, latent tuberculosis infection.

Table 3. Predictors for mortality outcome due to tuberculosis (N = 5,674)

No	Predictors	Mortality due to TB		Univariate analysis		Multivariate analysis*	
		No (n=5,562; %)	Yes (n=112; %)	OR (95%CI)	p-value	aOR (95% CI)	p-value
1	**Socio-demographic characteristics**						
	Male	3354 (60.3)	72 (64.3)	1.19 (0.80-1.75)	0.39	Not included	-
	Age (years)				0.000		0.000
	18–24	863 (15.5)	4 (3.6)	0.31 (0.11-0.86)		0.45 (0.13-1.52)	
	25–74	4184 (75.2)	62 (55.4)	Ref		Ref.	
	75–84	389 (7)	33 (29.5)	5.73 (3.71-8.84)		5.58 (3.10-10.03)	
	≥85	126 (2.3)	13 (11.6)	6.96 (3.73-12.99)		9.35 (4.31-20.30)	
	Born in the Netherlands**	1560 (28.1)	57 (51.8)	2.75 (1.88-4.02)	0.000	1.26 (0.75-2.12)	0.38
	Urban domicile	1954 (35.1)	43 (38.4)	1.15 (0.78-1.69)	0.47	Not included	-
2	**Current TB diagnosis**						
	Pulmonary diagnosis				0.000		0.038
	ETB	1876 (33.7)	14 (12.5)	Ref.		Ref.	
	PTB	2951 (53.1)	61 (54.5)	2.77 (1.55-4.97)		4.04 (0.92-17.75)	
	ETB + PTB	735 (13.2)	37 (33)	6.75 (3.63-12.55)		4.97 (1.42-17.41)	
	Initial TB location				0.000		0.000
	Lungs	3432 (61.7)	73 (65.2)	5.98 (2.75-13.01)		2.03 (0.45-9.04)	
	Central nervous system	57 (1)	13 (11.6)	64.09 (24.64-166.68)		120 (34.43-418.54)	
	Miliary	106 (1.9)	19 (17)	50.37 (20.72-122.45)		10.73 (2.50-46.02)	
	Others	1967 (35.4)	7 (6.3)	Ref.		Ref.	
	TB diagnosis outside of the Netherlands	49 (0.9)	1 (0.9)	1.01 (0.14-7.41)	0.98	Not included	-
3	**History of TB disease & treatment**						
	Previously diagnosed TB**	347 (6.7)	11 (14.5)	2.35 (1.23-4.49)	0.008	1.23 (0.61-2.48)	0.57
	Previously treated LTBI**	182 (3.5)	2 (2.7)	0.76 (0.18-3.10)	0.69	Not included	-
4	**Risk group of TB**						
	TB contact	371 (6.7)	4 (3.6)	0.52 (0.19-1.4)	0.19	Not included	-
	Immigrants and asylum seekers	994 (17.9)	3 (2.7)	0.13 (0.04-0.40)	0.000	0.11 (0.01-0.84)	0.03
	Illegal immigrants	200 (3.6)	1 (0.9)	0.24 (0.034-1.74)	0.19	Not included	-
	Homeless individuals	127 (2.3)	5 (4.5)	2.00 (0.80-4.99)	0.19	Not included	-
	Health care workers	45 (0.8)	1 (0.9)	1.10 (0.15-8.08)	0.60	Not included	-
	Travelers from/in endemic	128 (2.3)	2 (1.8)	0.77 (0.18-3.16)	0.72	Not included	

	area >3 month						
	Prisoners	143 (2.6)	0 (0)	0.17 (0.01-2.71)	0.21	Not included	-
	Alcohol addicts	109 (2)	2 (1.8)	0.91 (0.22-3.73)	0.89	Not included	-
	Drug addicts	146 (2.6)	6 (5.4)	2.10 (0.91-4.86)	0.12	3.56 (1.34-9.47)	0.01
5	**Comorbidities**						
	Diabetes	256 (4.6)	12 (10.7)	2.49 (1.35-4.59)	0.003	1.10 (0.46-2.65)	0.84
	Malignancy	128 (2.3)	7 (6.3)	2.83 (1.29 -6.20)	0.017	2.13 (0.89-5.11)	0.89
	Renal insufficiency/dialysis	82 (1.5)	9 (8)	5.84 (2.86-11.94)	0.000	3.23 (1.17-8.96)	0.024
	Organ transplantation	19 (0.3)	3 (2.7)	8.03 (2.34-27.53)	0.009	1.88 (0.18-19.54)	0.60

Notes: * Number of analysed cases 5,674, Hosmer & Lemeshow test 0.59, area under curve 0.85 (0.82-0.88); n/a, not applicable due to a small number of event; Ref., reference; OR, odds ratio; aOR, adjusted odds ratio; **missing value: Country of birth 15 (0.3%), previously diagnosed TB 437 (7.7%), previously treated LTBI 466 (8.21%); ETB, extra-pulmonary tuberculosis; PTB, pulmonary tuberculosis; TB, tuberculosis; LTBI, latent tuberculosis infection.